

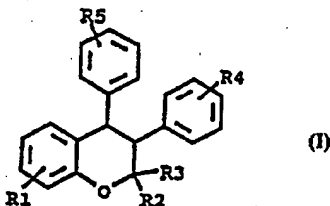
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## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(71) Applicant (for all designated States except US): NOVO NORDISK A/S [DK/DK]; Nove Allé, DK-2880 Bagsværd (DK).			
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(54) Title: USE OF 3,4-DIPHENYL CHROMANS FOR THE MANUFACTURE OF A PHARMACEUTICAL COMPOSITION FOR THE TREATMENT OF PROPHYLAXIS OF IDIOPATHIC OR PHYSIOLOGIC GYNAECOMASTIA



## (57) Abstract

The present invention provides novel uses of compounds of general formula (I) wherein R1, R4 and R5 are individually hydrogen, hydroxy, halogen, trifluoromethyl, lower alkyl, lower alkoxy or (tertiary amino)(lower alkoxy); and R2 and R3 are individually hydrogen or lower alkyl, or as a pharmaceutically acceptable salt thereof in combination with a pharmaceutically acceptable carrier for the manufacture of a pharmaceutical composition for the treatment or prophylaxis of idiopathic or physiologic gynaecomastia.

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(74) Common Representative: <b>NOVO NORDISK A/S; Corporate Patents, Novo Allé, DK-2880 Bagsværd (DK).</b>			
(54) Title: <b>USE OF 3,4-DIPHENYL CHROMANS FOR THE MANUFACTURE OF A PHARMACEUTICAL COMPOSITION FOR THE TREATMENT OF PROPHYLAXIS OF IDIOPATHIC OR PHYSIOLOGIC GYNAECOMASTIA</b>			
<div style="text-align: center;"><p>(I)</p></div>			
(57) Abstract			
<p>The present invention provides novel uses of compounds of general formula (I) wherein R1, R4 and R5 are individually hydrogen, hydroxy, halogen, trifluoromethyl, lower alkyl, lower alkoxy or (tertiary amino)(lower alkoxy); and R2 and R3 are individually hydrogen or lower alkyl, or as a pharmaceutically acceptable salt thereof in combination with a pharmaceutically acceptable carrier for the manufacture of a pharmaceutical composition for the treatment or prophylaxis of idiopathic or physiologic gynaecomastia.</p>			

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FR	France	MN	Mongolia	UZ	Uzbekistan
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- 5     Use of 3,4-diphenyl chromans for the manufacture of a pharmaceutical composition for the treatment or prophylaxis of idiopathic or physiologic gynaecomastia

#### FIELD OF THIS INVENTION

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The present invention relates to the use of compounds of the general formula I for the treatment of patients suffering from idiopathic or physiologic gynaecomastia and prophylaxis hereof. The present invention also embraces pharmaceutical compositions comprising these compounds and methods of using the compounds and their pharmaceutical compositions.

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#### BACKGROUND OF THIS INVENTION

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Gynaecomastia is characterised by an increased amount of breast tissue in males. A central issue in the evaluation of breast tissue in adult men is the separation of the normal from the abnormal. In autopsy data (Anderson JA & Groom JB, Acta Pathol Microbiol Immunol Scand 90:191, 1982) the incidence of active gynaecomastia is between 5% and 9%. However, it has been reported (Nuttall FQ, J Clin Endocrinol Metab 48:338, 1979; Niewoehner CV & Nuttall FQ, Am J Med 77:633, 1984) that approximately 40% of normal men and up to 70% of hospitalized men have palpable breast tissue. The reason for this discrepancy is not clear, but it may suggest that it can be difficult to distinguish true breast tissue from masses of adipose tissue without breast tissue (lipomastia). Alternatively, a true increase in the incidence of gynaecomastia may have taken place, or the autopsy data may underestimate the

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frequency of palpable breast tissue.

Histologically, early gynaecomastia is characterized by proliferation in the breast of both the fibroblastic stroma and the duct system, which  
5 elongates, buds, and duplicates. As gynaecomastia persists, progressive fibrosis and hyalination are associated with regression of epithelial proliferation. Eventually the number of ducts decreases. Resolution occurs by reduction in size and epithelial content with gradual disappearance of the ducts leaving hyaline bands that eventually disappears.

10 Growth of the breast in men, as in women, is mediated by estrogen and results from disturbances of the normal ratio of active androgen to estrogen in plasma or within the breast itself. Estradiol formation in the normal man occurs principally by the conversion of the circulating  
15 androgens to estrogens in peripheral tissues; the normal ratio of production of testosterone to estradiol in adult men is approximately 100:1 (6 mg versus 45  $\mu$ g), and the normal ratio of the two hormones in plasma is about 300:1. Feminization results when there is a significant decrease in this effective ratio as a result of diminished testosterone production or  
20 action, enhanced estrogen production, or both processes occurring simultaneously. The predominant manifestation of feminization in men is enlargement of the breast.

25 Enlargement of the male breast can occur as a normal physiologic phenomenon at certain stages of life or as the result of different pathologic conditions.

30 Physiologic gynaecomastia occur in newborns and adolescents as transient enlargements of the breast which normally disappears spontaneously within few weeks to years usually without leaving palpable changes.

Gynaecomastia of aging occurs in otherwise healthy men. Forty percent or more of aged men have gynaecomastia. A likely explanation is the

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increase with age in the conversion of androgens to estrogens in the extraglandular tissues. Abnormal liver function or drug therapy may be contributing causes to gynaecomastia in such men.

- 5 Pathologic gynaecomastia can result from one of three basic mechanisms: deficiency in testosterone production or action (with or without a secondary increase in estrogen production), increase in estrogen production, or drugs.
- 10 When the primary cause of the overestrogenization can be identified and corrected, the breast enlargement usually subsides promptly and eventually disappears. However, in a number of cases no cause can be found and the gynaecomastia is called idiopathic or physiologic. These cases can in some persons at certain stages of life cause tremendous psychological disturbances. The cause in these cases is always an increased
- 15 ratio of oestrogen/testosterone. There can be an increased risk of developing breast cancer under these circumstances. Surgery is undesirable in these otherwise healthy men. The most rational way to treat gynaecomastia would be to inhibit the underlying excess stimulation of
- 20 breast tissue by endogenous oestrogen and to induce atrophy of the breast tissue.
- Centchroman is a non-steroidal compound known to have antiestrogenic activity. It is in use in India as an oral contraceptive (see, for example,
- 25 Salman et al., U.S. Patent Specification No. 4,447,622; Singh et al., Acta Endocrin (Copenh) 126 (1992), 444 - 450; Grubb, Curr Opin Obstet Gynecol 3 (1991), 491 - 495; Sankaran et al., Contraception 9 (1974), 279 - 289; Indian Patent Specification No. 129187). Centchroman has also been investigated as an anti-cancer agent for treatment of
- 30 advanced breast cancer (Misra et al., Int J Cancer 43 (1989), 781 - 783. Recently, centchroman as a racemate has been found potent as a cholesterol lowering pharmaceutical expressed by a significant decrease

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of the serum concentrations (S.D. Bain et al., J Min Bon Res 9 (1994), S 394).

5 U.S. patent 5,280,040 describes methods and pharmaceutical compositions for reducing bone loss using 3,4-diarylchromans and their pharmaceutically acceptable salts.

There remains today a need in the art for compositions and methods that are useful in the treatment or prophylaxis of idiopathic or physiologic  
10 gynaecomastia.

One object of the present invention is to provide compounds which can effectively be used in the treatment or prophylaxis of idiopathic or physiologic gynaecomastia.  
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#### BRIEF DESCRIPTION OF THIS INVENTION

It has, surprisingly, been found that compounds of the general formula I as stated in claim 1 can be used in the treatment or prophylaxis of  
20 idiopathic or physiologic gynaecomastia.

#### DETAILED DESCRIPTION OF THIS INVENTION

The present invention is based in part on the discovery that a representative 3,4-diarylchroman, centchroman (3,4-trans-2,2-dimethyl-3-phenyl-4-  
25 [p-(beta-pyrrolidinoethoxy)phenyl]-7-methoxychroman) is effective against idiopathic or physiologic gynaecomastia, inter alia in rats. These animal models are generally recognized models of idiopathic or physiologic gynaecomastia. These data thus indicate that the 3,4-diaryl-  
30 chromans are useful as therapeutic or preventive agents against idiopathic or physiologic gynaecomastia in mammals, including primates such as humans.

Within the present invention, compounds of formula I as stated in claim 1 are used for idiopathic or physiologic gynaecomastia in a patient. Within formula I, R1, R4 and R5 are individually hydrogen, halogen, trifluoromethyl, lower alkyl, lower alkoxy or (tertiary amino)(lower alkoxy); and R2 and R3 are individually hydrogen or a lower alkyl. As used herein, the term "lower alkyl" includes straight and branched chain alkyl radicals containing from 1 to 6 carbon atoms, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, tert-butyl, n-amyl, sec-amyl, n-hexyl, 2-ethylbutyl, 2,3-dimethylbutyl and the like. The term "lower alkoxy" includes straight and branched chain alkoxy radicals containing from 1 to 6 carbon atoms, such as methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, tert-butoxy, n-amyl, sec-amyl, n-hexyloxy, 2-ethylbutoxy, 2,3-dimethylbutoxy and the like. "Halogen" includes chloro, fluoro, bromo and iodo. The tertiary amino radical may be a dialkylamine such as a dimethyl, diethyl, dipropyl, dibutyl or a polymethyleneimine, e.g. piperidine, pyrrolidine, N-methylpiperazine or morpholine. Preferred compounds include those in which R1 is lower alkoxy; R2 and R3 are lower alkyl, especially methyl; R4 is hydrogen; and R5 is (tertiary amino)(lower alkoxy) of the polymethyleneimine type. Within particularly preferred embodiments, R1 is in the 7-position and is lower alkoxy, particularly methoxy; each of R2 and R3 is methyl, R4 is hydrogen and R5 is in the 4-position and is a (tertiary amino)(lower alkoxy) radical such as pyrrolidinoethoxy. To be included by this invention are all pharmaceutically acceptable salts of the mentioned compounds of formula I.

It is preferred to use the compounds of formula I in the transconfiguration. These compounds may be used as racemic mixtures, or the isolated d- or l- enantiomers may be used. The trans-l-enantiomers are more preferred.

A particularly preferred compound for use within the present invention is centchroman having the formula IV as stated in the claims below.



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Although only one enantiomer is shown, it will be understood that the formula IV is used herein to designate the transconfiguration of the 3- and 4-phenyl groups and that both the d- and l-enantiomers, as well as the racemic mixture, are included.

5

3,4-diarylchromans are prepared according to known methods, such as those disclosed in U.S. Patent Specification No. 3,340,276 to Carney et al., U.S. Patent Specification No. 3,822,287 to Bolger, and Ray et al., J Med Chem **19** (1976), 276 - 279, the contents of which are incorporated herein by reference. Conversion of the cis isomer to the trans configuration by means of an organometallic base-catalyzed rearrangement is disclosed in U.S. Patent Specification No. 3,822,287. The optically active d- and l-enantiomers may be prepared as disclosed by Salman et al. in U.S. Patent Specification No. 4,447,622 (incorporated herein by reference) by forming an optically active acid salt which is subjected to alkaline hydrolysis to produce the desired enantiomer.

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Within the present invention, 3,4-diarylchromans may be prepared in the form of pharmaceutically acceptable salts, especially acid-addition salts, including salts of organic acids and mineral acids. Examples of such salts include salts of organic acids such as formic acid, fumaric acid, acetic acid, propionic acid, glycolic acid, lactic acid, pyruvic acid, oxalic acid, succinic acid, malic acid, tartaric acid, citric acid, benzoic acid, salicylic acid and the like. Suitable inorganic acid-addition salts include salts of hydrochloric, hydrobromic, sulphuric and phosphoric acids and the like. The acid addition salts may be obtained as the direct products of compound synthesis. In the alternative, the free base may be dissolved in a suitable solvent containing the appropriate acid, and the salt isolated by evaporating the solvent or otherwise separating the salt and solvent.

3,4-diarylchromans and their salts are useful within human and veterinary medicine, for example, in the treatment of patients suffering from

idiopathic or physiologic gynaecomastia. For use within the present invention, 3,4-diarylchromans and their pharmaceutically acceptable salts are formulated with a pharmaceutically acceptable carrier to provide a medicament for parenteral, oral, nasal, rectal, subdermal or intradermal or transdermal administration according to conventional methods.

Formulations may further include one or more diluents, fillers, emulsifiers, preservatives, buffers, excipients, etc. and may be provided in such forms as liquids, powders, emulsions, suppositories, liposomes, transdermal patches, controlled release, dermal implants, tablets, etc.

One skilled in this art may formulate the compounds in an appropriate manner, and in accordance with accepted practices, such as those disclosed in Remington's Pharmaceutical Sciences, Gennaro, ed., Mack Publishing Co., Easton, PA, 1990.

Oral administration is preferred. Thus, the active compound is prepared in a form suitable for oral administration, such as a tablet or capsule.

Typically, a pharmaceutically acceptable salt of the compound is combined with a carrier and moulded into a tablet. Suitable carriers in this regard include starch, sugars, dicalcium phosphate, calcium stearate, magnesium stearate and the like. Such compositions may further include one or more auxiliary substances, such as wetting agents, emulsifiers, preservatives, stabilizers, colouring additives, etc.

Pharmaceutical compositions are administered one or more times per day or week. An effective amount of such a pharmaceutical composition is the amount that provides a clinically significant effect against idiopathic or physiologic gynaecomastia. Such amounts will depend, in part, on the particular condition to be treated, age, weight, and general health of the patient, and other factors evident to those skilled in the art.

The pharmaceutical compositions may be administered in unit dosage form one or more times per day or week. In the alternative, they may be

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provided as controlled release formulations suitable for dermal implantation. Implants are formulated to provide release of active compound over the desired period of time, which can be up to several years. Controlled-release formulations are disclosed by, for example, Sanders et al., J Pharm Sci **73** (1964), 1294 - 1297, 1984; U.S. Patent Specification No. 4,489,056; and U.S. Patent Specification No. 4,210,644, which are incorporated herein by reference.

The following examples are offered by way of illustration, not limitation.

Examples of preferred compounds are centchroman as a racemic mixture and as l-centchroman and d-centchroman. Furthermore, 3,4-trans-2,2-dimethyl-3-phenyl-4-[4-(2-(pyrrolidin-1-yl)ethoxy)phenyl]-7-hydroxychroman is a preferred compound.

A more preferred compound is trans-l-centchroman (l-3,4-trans-2,2-dimethyl-3-phenyl-4-[p-(beta-pyrrolidinoethoxy)phenyl]-7-methoxychroman).

Examples of pharmaceutically acceptable acid addition salts are salts with non-toxic acids, either inorganic acids such as hydrochloric acid, sulphuric acid and phosphoric acid, or organic acids such as formic acid, fumaric acid, acetic acid, propionic acid, succinic acid, gluconic acid, lactic acid, citric acid, ascorbic acid, benzoic acid, embonic acid, methanesulphonic acid and malonic acid.

The present invention is further illustrated by the following examples which, however, are not to be construed as limiting the scope of protection. The features disclosed in the foregoing description and in the following examples may, both separately and in any combination thereof, be material for realising the invention in diverse forms thereof.

## EXAMPLES

## Test 1

5 The competitive antiestrogenic action of centchroman has been demonstrated in uterine tissue from normal sexually mature Sprague-Dawley rats.

10 Twenty Sprague-Dawley sexually mature female rats (200-225 g) were obtained from Mollegaards breeding center, LI Skensved, Denmark. The rats were housed in metal hanging cages in groups of two and had ad libitum access to food and water for one week. Room temperature was maintained at  $20^{\circ} \pm 1.5^{\circ}$  with a minimum relative humidity of 40%. The photoperiod in the room was 12 hours light and 12 hours dark.

15 After the one week of acclimation period the rats were at random divided into five treatment groups of each 4 rats and daily oral treatment with the test compound was initiated. The test compound was given in five doses (0 mg/kg/day, 5 mg/kg/day, 10 mg/kg/day, 25 mg/kg/day or 75 mg/kg /day) for fourteen days. Following the dosing period the animals were weighed and sacrificed by asphyxiation with CO<sub>2</sub>, the uterus was removed through a midline incision, and a wet uterine weight was determined after gently blotting on a towel.

25 Data shown in table I below shows comparative results among the treated rats. Treatment with centchroman in sexually mature rats with intact ovaries induce a significant hypoplasia of the uteri.

Table I.

Group	Body weight (g)	Uterus weight (g)	Uterus/body (mg/g)
0 mg/kg/day	182	0.49	2.71
5 mg/kg/day	159	0.18	1.15
10 mg/kg/day	165	0.21	1.25
25 mg/kg/day	153	0.20	1.30
75 mg/kg/day	135	0.18	1.32

10 From this observation it can be concluded that centchroman acts as an antagonist to the normal stimulating effect of oestrogen on the uterus. This was supported by the subsequent microscopy, which revealed an atrophic endometrium in these rats.

15 Test 2

Between 3 and 25 men having gynaecomastia are administered a compound of the present invention. The amount of compound administered is from 0.1 to 1000 mg/day, and the period of administration is 3 months.

20

The men are observed during the period of administration, and up to 3 months after discontinuance of administration, for effects on the gynaecomastia.

25 Test 3

The same procedure as is used in Test 1, except for the period of administration is 6 months.

Test 4

30 The same procedure as is used in Test 1, except for the period of

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administration is 1 year.

#### Test 5

5 Prolonged estrogen stimulation is used to induce gynaecomastia in sexually mature male rats. Animals are dosed with estradiol 3-5 times per week by injection for 2-4 months until gynaecomastia arise. Treatment consisting of a compound of the invention or vehicle is administered daily for 3-20 weeks and then animals are sacrificed and the mammary glands harvested and analyzed for regression of

10 gynaecomastia.

#### Test 6

Tissue from human mammary glands are harvested and maintained, in vitro, as primary non-transforming cultures. Surgical specimens are

15 pushed through a sterile mesh or sieve, or alternatively teased apart from surrounding tissue to produce a single cell suspension. Cells are maintained in media containing 10% serum and antibiotic. Rates of growth in the presence or absence of estrogen are determined. Cells are assayed for their ability to respond to growth factors and growth hormone. Levels

20 of steroid hormones receptors are assessed weekly to determine whether important cell characteristics are maintained in vitro. Tissue from 5-25 patients are utilized.

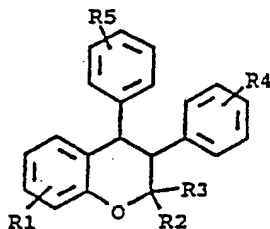
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CLAIMS

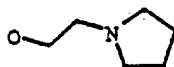
1. The use of compounds of the general formula I



- wherein R1, R4 and R5 are individually hydrogen, hydroxy, halogen, trifluoromethyl, lower alkyl, lower alkoxy or (tertiary amino)(lower alkoxy); and R2 and R3 are individually hydrogen or lower alkyl, or as a pharmaceutically acceptable salt thereof in combination with a pharmaceutically acceptable carrier for the manufacture of a pharmaceutical composition for the treatment or prophylaxis of idiopathic or physiologic gynaecomastia.
2. The use, according to claim 1, wherein R1 in the compound used is lower alkoxy, R2 and R3 are lower alkyl, R4 is hydrogen and R5 is tertiary amino lower alkoxy.
3. The use according to claim 1 wherein R1 is methoxy.
4. The use according to claim 1 wherein R2 is methyl.
5. The use according to claim 1 wherein R3 is methyl.

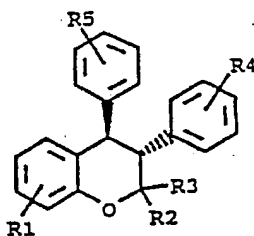
- 13 -

6. The use according to claim 1 wherein R4 is hydrogen.
7. The use according to claim 1 wherein R5 is a group as stated in formula II below:



(II)

8. The use according to claim 1 wherein said compound is an isolated d- or l-enantiomer.
9. The use according to claim 1 wherein said compound has the general formula III as stated below:



(III)

10. The use according to anyone of the preceding claims wherein said compound is an isolated l-enantiomer.

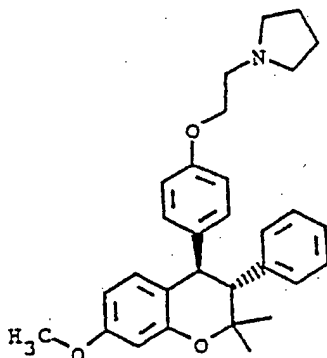


- 14 -

11. The use according to claim 1 wherein said compound is centchroman having the formula IV as stated below:

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(IV)

12. The use according to claim 11 wherein said compound is an isolated d- or l-enantiomer.

13. The use according to claim 11 wherein said compound is an isolated l-enantiomer.

14. The use according to claim 1 wherein said composition is in a form suitable for oral administration.

15. The use according to claim 1 wherein said compound is administered as a dose in a range from about 0.001 to 75, preferably in a range from about 0.01 to 75, more preferably in the range from about 0.01 to 50 and especially in the range from about 0.1 to 25 mg/kg patient per day.

16. The use according to claim 1 wherein said composition is administered one or more times per day or week.

17. The use according to claim 1 wherein said composition is in the

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form of a dermal implant.

18. Method for treatment and prophylaxis of idiopathic or physiologic gynaecomastia comprising administering to a patient a clinically effective amount of a compound of formula 1 as stated in claim 1 or an isolated d- or l-enantiomer of an idiopathic or physiologic gynaecomastia therapeutic or preventive compound of the formula I stated to be used in any one of the preceding use claims, or a pharmaceutically acceptable salt thereof in an amount sufficient to treat or prevent idiopathic or physiologic gynaecomastia.
19. A method of treating or preventing idiopathic or physiologic gynaecomastia which method comprises administering a clinically effective amount of compounds and pharmaceutically acceptable compositions, according to previous claims to a patient in need of such a treatment.
20. Any novel feature or combination of features described herein.

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/DK 96/00012

<b>A. CLASSIFICATION OF SUBJECT MATTER</b>		
IPC6: A61K 31/40, A61K 31/35 According to International Patent Classification (IPC) or to both national classification and IPC		
<b>B. FIELDS SEARCHED</b>		
Minimum documentation searched (classification system followed by classification symbols)		
IPC6: A61K		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
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Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)		
CAS-ONLINE		
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Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
<input type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/> See patent family annex.		
<p>* Special categories of cited documents:</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</p> <p>"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art</p> <p>"&amp;" document member of the same patent family</p>		
Date of the actual completion of the international search		Date of mailing of the international search report
15 March 1996		29 - 04 - 1996
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. + 46 8 666 02 86		Authorized officer  Göran Karlsson Telephone No. + 46 8 782 25 00

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/DK 96/00012

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 18-19  
because they relate to subject matter not required to be searched by this Authority, namely:  
A method for treatment of the human or animal body by therapy,  
see rule 39.1.
2. ☒ Claims Nos.: 20  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:  
Claim 20 is obscure and does not clearly define the matter for which protection is sought, see Article 6.
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.  
☐ No protest accompanied the payment of additional search fees.

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